

(43) International Publication Date: 9 May 1997 (09.05.97)

Date of publication of the amended claims and statement:
26 June 1997 (26.06.97)

$$\begin{array}{c}
 R_1 \quad R_1 \quad (R_2)_m \\
 \diagup \quad \diagdown \quad \diagup \\
 (R_3)_o - \text{C}_6\text{H}_3 - \text{S(O)}_p - Y(R_2) - A - B \quad (1) \\
 \diagdown \quad \diagup \quad \diagdown \\
 \quad \quad \quad X
 \end{array}$$

Compounds of formula (1) wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or X is [C(R₁)_n] where n is an integer between 0 and 2; R₁ is independently H or alkyl of 1 to 6 carbons; R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons; R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F; m is an integer having the value of 0-3; o is an integer having the value of 0-4; p is an integer having the value of 0-2; Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups; A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, are selective agonists of RXR retinoid receptors.

FOR THE PURPOSES OF INFORMATION ONLY

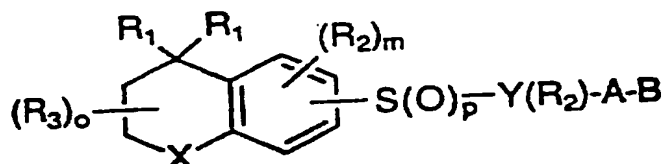
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

AMENDED CLAIMS

[received by the International Bureau on 5 May 1997 (05.05.97) ;
original claims 6-9 and 15-24 cancelled ;
original claims 1 and 11 amended ;
remaining claims unchanged (4 pages)]

1. (AMENDED) A compound of the formula



wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons,

or

X is $[C(R_1)_2]_n$ where n is an integer between 0 and 2;

R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4;

p is an integer having the value of 0 - 2;

Y is heteroaryl selected from a group consisting of pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said heteroaryl groups being optionally substituted with one or two R₂ groups;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons

1 and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple
2 bonds, and

3 B is hydrogen, COOH or a pharmaceutically acceptable salt
4 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO,
5 CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower
6 alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1
7 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or
8 (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a
9 cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower
10 alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of
11 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or
12 lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is
13 lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.

14 2. A compound in accordance with Claim 1 wherein X is
15 [C(R₁)₂]_n and n is 1.

16 3. A compound in accordance with Claim 1 wherein X is S.

17 4. A compound in accordance with Claim 1 wherein X is O.

18 5. A compound in accordance with Claim 1 wherein X is
19 NR'.

20 6. (CANCELED)

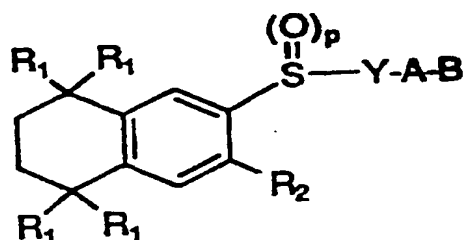
21 7. (CANCELED)

22 8. (CANCELED)

23 9. (CANCELED)

24 10. A compound in accordance with Claim 1 wherein Y is
25 thiazolyl.

11. (AMENDED) A compound of the formula



wherein R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, or fluoro substituted alkyl of 1 to 6 carbons;

Y is thiazolyl;

p is an integer having the value of 0 - 2;

A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, and

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.

1 12. A compound in accordance with Claim 11 wherein the R_1
2 groups are methyl.

3 13. A compound in accordance with Claim 12 wherein R_2 is H
4 or CH_3 .

5 14. A compound in accordance with Claim 13 wherein A is
6 $(CH_2)_q$ where q is 0 and wherein B is COOH or a pharmaceutically
7 acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

8 15. (CANCELED)

9 16. (CANCELED)

10 17. (CANCELED)

11 18. (CANCELED)

12 19. (CANCELED)

13 20. (CANCELED)

14 21. (CANCELED)

15 22. (CANCELED)

16 23. (CANCELED)

17 24. (CANCELED)

18 25. A compound in accordance with Claim 14 wherein Y is
19 2-thiazolyl substituted in the 5 position with the A-B group.

20 26. A compound in accordance with Claim 25 wherein p is
21 zero.

22 27. A compound in accordance with Claim 26 which is ethyl
23 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-5-thiazolecar
24 boxylate and 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
25 naphthylthio)-5-thiazolecarboxylic acid.

STATEMENT UNDER ARTICLE 19

The International Search Report mailed on March 4, 1997, cited several documents in category X, over which the subject matter of the claims was deemed not novel or not inventive.

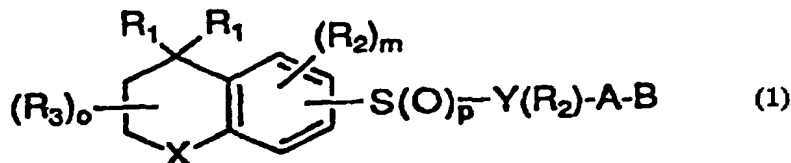
Claims 1 and 11 were amended, and Claims 6 - 9 and 15 - 24 were canceled so as to avoid the subject matter of the cited references.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 323/62, 317/44, C07D 213/80, 277/56, A61K 31/235, 31/455, 31/425		A1	(11) International Publication Number: WO 97/16422
			(43) International Publication Date: 9 May 1997 (09.05.97)
(21) International Application Number: PCT/US96/17295		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 29 October 1996 (29.10.96)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 08/552,965 1 November 1995 (01.11.95) US			
(71) Applicant: ALLERGAN [US/US]; 8301 Mars Drive, Waco, TX 76712 (US).			
(72) Inventors: BEARD, Richard, L.; 2341 Azure Avenue, Newport Beach, CA 92660 (US). COLON, Diana, F.; 247 Veneto, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US).			
(74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (US).			

(54) Title: **SULFIDES, SULFOXIDES AND SULFONES DISUBSTITUTED WITH A TETRAHYDRONAPHTHALENYL, CHROMANYL, THIOCHROMANYL OR TETRAHYDROQUINOLINYL AND SUBSTITUTED PHENYL OR HETEROARYL GROUP, HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY**



(57) Abstract

Compounds of formula (1) wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or X is [C(R₁)₂]_n where n is an integer between 0 and 2; R₁ is independently H or alkyl of 1 to 6 carbons; R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons; R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F; m is an integer having the value of 0-3; o is an integer having the value of 0-4; p is an integer having the value of 0-2; Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups; A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, are selective agonists of RXR retinoid receptors.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**SULFIDES, SULFOXIDES AND SULFONES DISUBSTITUTED
WITH A TETRAHYDRONAPHTHALENYL, CHROMANYL,
THIOCHROMANYL OR TETRAHYDROQUINOLINYL AND
SUBSTITUTED PHENYL OR HETEROARYL GROUP, HAVING
RETINOID-LIKE BIOLOGICAL ACTIVITY**

1. Field of the Invention

The present invention relates to novel compounds having retinoid-like biological activity. More specifically, the present invention relates to sulfide, sulfoxide and sulfone compounds disubstituted with a tetrahydronaphthalenyl, chromanyl, thiochromanyl or tetrahydroquinoliny and substituted phenyl or heteroaryl group having retinoid-like biological activity.

2. Background Art

Compounds which have retinoid-like activity are well known in the art, and are described in numerous United States and other patents and in scientific publications. It is generally known and accepted in the art that retinoid-like activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having a retinoid-like compound or compounds as the active ingredient are useful as regulators of cell proliferation and differentiation, and particularly as agents for treating skin-related diseases, including, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical

1 anti-microbial, as skin anti-pigmentation agents and to treat and reverse
2 the effects of age and photo damage to the skin. Retinoid compounds
3 are also useful for the prevention and treatment of cancerous and
4 precancerous conditions, including, premalignant and malignant
5 hyperproliferative diseases such as cancers of the breast, skin, prostate,
6 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral
7 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
8 leukoplakias and papillomas of the mucous membranes and in the
9 treatment of Kaposi's sarcoma. In addition, retinoid compounds can be
10 used as agents to treat diseases of the eye, including, without limitation,
11 proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and
12 other corneopathies, as well as in the treatment and prevention of
13 various cardiovascular diseases, including, without limitation, diseases
14 associated with lipid metabolism such as dyslipidemias, prevention of
15 post-angioplasty restenosis and in the treatment and prevention of
16 diabetes and obesity and as an agent to increase the level of circulating
17 tissue plasminogen activator (TPA). Other uses for retinoid compounds
18 include the prevention and treatment of conditions and diseases
19 associated with human papilloma virus (HPV), including warts and
20 genital warts, various inflammatory diseases such as pulmonary fibrosis,
21 ileitis, colitis and Krohn's disease, neurodegenerative diseases such as
22 Alzheimer's disease, Parkinson's disease and stroke, improper pituitary
23 function, including insufficient production of growth hormone,
24 modulation of apoptosis, including both the induction of apoptosis and
25 inhibition of T-Cell activated apoptosis, restoration of hair growth,
26 including combination therapies with the present compounds and other
27 agents such as Minoxidil^R, diseases associated with the immune system,
28 including use of the present compounds as immunosuppressants and

1 immunostimulants, modulation of organ transplant rejection and
2 facilitation of wound healing, including modulation of chelosis.

3 United States Patent Nos. 4,740,519 (Shroot et al.), 4,826,969
4 (Maignan et al.), 4,326,055 (Loeliger et al.), 5,130,335 (Chandraratna et
5 al.), 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et al.), 5,324,840
6 (Chandraratna), 5,344,959 (Chandraratna), 5,130,335 (Chandraratna et
7 al.), Published European Patent Application Nos. 0 176 034 A (Wuest
8 et al.), 0 350 846 A (Klaus et al.), 0 176 032 A (Frickel et al.), 0 176
9 033 A (Frickel et al.), 0 253 302 A (Klaus et al.), 0 303 915 A (Bryce et
10 al.), UK Patent Application GB 2190378 A (Klaus et al.), German
11 Patent Application Nos. DE 3715955 A1 (Klaus et al.), DE 3602473 A1
12 (Wuest et al., and the articles J. Amer. Acad. Derm. 15: 756 - 764
13 (1986) (Sporn et al.), Chem. Pharm. Bull. 33: 404-407 (1985) (Shudo et
14 al.), J. Med Chem. 1988 31, 2182 - 2192 (Kagechika et al.), Chemistry
15 and Biology of Synthetic Retinoids CRC Press Inc. 1990 p 334 - 335,
16 354 (Dawson et al.), describe or relate to compounds which include a
17 tetrahydronaphthyl moiety and have retinoid-like or related biological
18 activity. United States Patent No. 4,391,731 (Boller et al.) describes
19 tetrahydronaphthalene derivatives which are useful in liquid crystal
20 compositions.

21 United States Patent Nos. 4,980,369, 5,006,550, 5,015,658,
22 5,045,551, 5,089,509, 5,134,159, 5,162,546, 5,234,926, 5,248,777,
23 5,264,578, 5,272,156, 5,278,318, 5,324,744, 5,346,895, 5,346,915,
24 5,348,972, 5,348,975, 5,380,877, 5,399,561, 5,407,937, (assigned to the
25 same assignee as the present application) and patents and publications
26 cited therein, describe or relate to chroman, thiochroman and
27 1,2,3,4-tetrahydroquinoline derivatives which have retinoid-like
28 biological activity. Still further, several co-pending applications and

1 recently issued patents which are assigned to the assignee of the present
2 application, are directed to further compounds having retinoid-like
3 activity.

4 It is now general knowledge in the art that two main types of
5 retinoid receptors exist in mammals (and other organisms). The two
6 main types or families of receptors respectively designated the RARs
7 and RXRs. Within each type there are subtypes; in the RAR family
8 the subtypes are designated RAR α , RAR β and RAR γ , in RXR the
9 subtypes are: RXR α , RXR β and RXR γ . It has also been established in
10 the art that the distribution of the two main retinoid receptor types,
11 and of the several sub-types is not uniform in the various tissues and
12 organs of mammalian organisms. Moreover, it is generally accepted in
13 the art that many unwanted side effects of retinoids are mediated by
14 one or more of the RAR receptor subtypes. Accordingly, among
15 compounds having agonist-like activity at retinoid receptors, specificity
16 or selectivity for one of the main types or families, and even specificity
17 or selectivity for one or more subtypes within a family of receptors, is
18 considered a desirable pharmacological property.

19 The present invention provides further compounds having
20 retinoid-like biological activity and specifically compounds which are
21 specific or highly selective agonists of RXR retinoid receptors in
22 preference over RAR retinoid receptors.

23 SUMMARY OF THE INVENTION

24 The present invention covers compounds of Formula 1

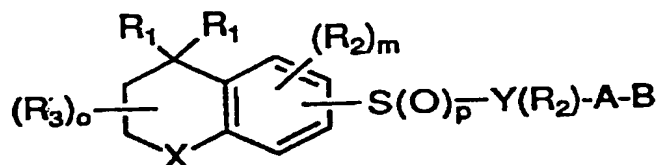
25

26

27

28

5



Formula 1

wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[\text{C(R}_1\text{)}_2]_n$ where n is an integer between 0 and 2;

R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4;

p is an integer having the value of 0 - 2;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolizyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups;

A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1

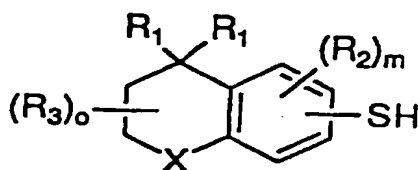
1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or
2 (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a
3 cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower
4 alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1
5 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower
6 alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower
7 alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

8 In a second aspect, this invention relates to the use of the
9 compounds of Formula 1 for the treatment of skin-related diseases,
10 including, without limitation, actinic keratoses, arsenic keratoses,
11 inflammatory and non-inflammatory acne, psoriasis, ichthyoses and
12 other keratinization and hyperproliferative disorders of the skin,
13 eczema, atopic dermatitis, Darriers disease, lichen planus, prevention
14 and reversal of glucocorticoid damage (steroid atrophy), as a topical
15 anti-microbial, as skin anti-pigmentation agents and to treat and reverse
16 the effects of age and photo damage to the skin. The compounds are
17 also useful for the prevention and treatment of cancerous and
18 precancerous conditions, including, premalignant and malignant
19 hyperproliferative diseases such as cancers of the breast, skin, prostate,
20 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral
21 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
22 leukoplakias and papillomas of the mucous membranes and in the
23 treatment of Kaposi's sarcoma. In addition, the present compounds can
24 be used as agents to treat diseases of the eye, including, without
25 limitation, proliferative vitreoretinopathy (PVR), retinal detachment,
26 dry eye and other corneopathies, as well as in the treatment and
27 prevention of various cardiovascular diseases, including, without
28 limitation, diseases associated with lipid metabolism such as

1 dyslipidemias, prevention of post-angioplasty restenosis and as an agent
2 to increase the level of circulating tissue plasminogen activator (TPA).
3 Other uses for the compounds of the present invention include the
4 prevention and treatment of conditions and diseases associated with
5 human papilloma virus (HPV), including warts and genital warts,
6 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis
7 and Krohn's disease, neurodegenerative diseases such as Alzheimer's
8 disease, Parkinson's disease and stroke, improper pituitary function,
9 including insufficient production of growth hormone, modulation of
10 apoptosis, including both the induction of apoptosis and inhibition of
11 T-Cell activated apoptosis, restoration of hair growth, including
12 combination therapies with the present compounds and other agents
13 such as Minoxidil^R, diseases associated with the immune system,
14 including use of the present compounds as immunosuppressants and
15 immunostimulants, modulation of organ transplant rejection and
16 facilitation of wound healing, including modulation of chelosis.

17 This invention also relates to a pharmaceutical formulation
18 comprising a compound of Formula 1 in admixture with a
19 pharmaceutically acceptable excipient.

20 In another aspect, this invention relates to processes for making a
21 compound of Formula 1 which processes comprise reacting a
22 compound of Formula 2, or a suitable salt such as a sodium salt of a
23 compound of Formula 2 with a compound of Formula 3 (where X₁ is
24 halogen and Y, R₂, A and B are defined as in connection with Formula
25 1) in the presence of base and preferably in the presence of a catalyst,
26 and also to the processes of oxidizing a sulfide compound of Formula 1
27 (p = 0) to the corresponding sulfoxide or sulfone compound of
28 Formula 1 (p = 1 or p = 2).



Formula 2

Formula 3

Still further, the present invention relates to such reactions performed on the compounds of Formula 1 which cause transformations of the B group while the reaction product still remains within the scope of Formula 1.

General Embodiments

Definitions

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and cycloalkenyl groups having one or more sites of unsaturation. Similarly, the term alkynyl refers to and covers normal alkynyl, and branch chain alkynyl groups having one or more triple bonds.

Lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons in case of normal lower alkyl, and as

1 applicable 3 to 6 carbons for lower branch chained and cycloalkyl
2 groups. Lower alkenyl is defined similarly having 2 to 6 carbons for
3 normal lower alkenyl groups, and 3 to 6 carbons for branch chained
4 and cyclo- lower alkenyl groups. Lower alkynyl is also defined similarly,
5 having 2 to 6 carbons for normal lower alkynyl groups, and 4 to 6
6 carbons for branch chained lower alkynyl groups.

7 The term "ester" as used here refers to and covers any compound
8 falling within the definition of that term as classically used in organic
9 chemistry. It includes organic and inorganic esters. Where B of
10 Formula 1 is -COOH, this term covers the products derived from
11 treatment of this function with alcohols or thioalcohols preferably with
12 aliphatic alcohols having 1-6 carbons. Where the ester is derived from
13 compounds where B is -CH₂OH, this term covers compounds derived
14 from organic acids capable of forming esters including phosphorous
15 based and sulfur based acids, or compounds of the formula
16 -CH₂OCOR₁₁ where R₁₁ is any substituted or unsubstituted aliphatic,
17 aromatic, heteroaromatic or aliphatic aromatic group, preferably with
18 1-6 carbons in the aliphatic portions.

19 Unless stated otherwise in this application, preferred esters are
20 derived from the saturated aliphatic alcohols or acids of ten or fewer
21 carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and
22 acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters
23 are those derived from lower alkyl acids and alcohols. Also preferred
24 are the phenyl or lower alkyl phenyl esters.

25 Amides has the meaning classically accorded that term in organic
26 chemistry. In this instance it includes the unsubstituted amides and all
27 aliphatic and aromatic mono- and di- substituted amides. Unless stated
28 otherwise in this application, preferred amides are the mono- and

1 di-substituted amides derived from the saturated aliphatic radicals of
2 ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic
3 radicals of 5 to 10 carbon atoms. Particularly preferred amides are
4 those derived from substituted and unsubstituted lower alkyl amines.
5 Also preferred are mono- and disubstituted amides derived from the
6 substituted and unsubstituted phenyl or lower alkylphenyl amines.
7 Unsubstituted amides are also preferred.

8 Acetals and ketals include the radicals of the formula-CK where
9 K is $(-OR)_2$. Here, R is lower alkyl. Also, K may be $-OR_7O-$ where R,
10 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

11 A pharmaceutically acceptable salt may be prepared for any
12 compound in this invention having a functionality capable of forming
13 such-salt, for example an acid functionality. A pharmaceutically
14 acceptable salt is any salt which retains the activity of the parent
15 compound and does not impart any deleterious or untoward effect on
16 the subject to which it is administered and in the context in which it is
17 administered. Pharmaceutically acceptable salts may be derived from
18 organic or inorganic bases. The salt may be a mono or polyvalent ion.
19 Of particular interest are the inorganic ions, sodium, potassium,
20 calcium, and magnesium. Organic salts may be made with amines,
21 particularly ammonium salts such as mono-, di- and trialkyl amines or
22 ethanol amines. Salts may also be formed with caffeine, tromethamine
23 and similar molecules. Where there is a nitrogen sufficiently basic as to
24 be capable of forming acid addition salts, such may be formed with any
25 inorganic or organic acids or alkylating agent such as methyl iodide.
26 Preferred salts are those formed with inorganic acids such as
27 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of
28 simple organic acids such as mono-, di- or tri- acid may also be used.

1 Some of the compounds of the present invention may have trans
2 and cis (E and Z) isomers. In addition, the compounds of the present
3 invention may contain one or more chiral centers and therefore may
4 exist in enantiomeric and diastereomeric forms. The scope of the
5 present invention is intended to cover all such isomers per se, as well as
6 mixtures of cis and trans isomers, mixtures of diastereomers and
7 racemic mixtures of enantiomers (optical isomers) as well.

8 With reference to the symbol Y in Formula 1, the preferred
9 compounds of the invention are those where Y is phenyl, pyridyl,
10 2-thiazolyl, thienyl, or furyl, even more preferably, phenyl, pyridyl and
11 2-thiazolyl. As far as substitutions on the Y (phenyl) and Y (pyridyl)
12 groups are concerned, compounds are preferred where the phenyl
13 group is 1,4 (para) substituted by the $S(=O)_p$ and A-B groups, and
14 where the pyridine ring is 2,5 substituted by the $S(=O)_p$ and A-B
15 groups. (Substitution in the 2,5 positions in the "pyridine"
16 nomenclature corresponds to substitution in the 6-position in the
17 "nicotinic acid" nomenclature.) When the Y group is thiazole it is
18 preferably substituted in the 2 position by the $S(=O)_p$ group and in the
19 5 position by the A-B group. In the preferred compounds of the
20 invention there is no optional R_2 substituent on the Y group.

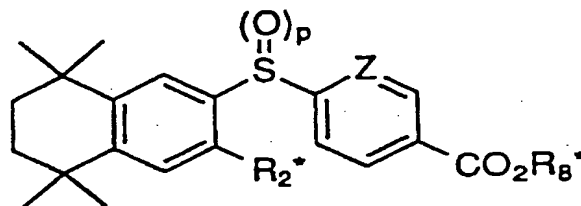
21 With reference to the symbol X in Formula 1, compounds are
22 preferred in accordance with the invention where X is $[C(R_1)_2]_n$ and n is
23 1, and also where X is O or S (chroman and thiochroman derivatives).
24 Even more preferred are compounds where X is $[C(R_1)_2]_n$ and n is 1
25 (tetrahydronaphthalene derivatives). The presently preferred
26 compounds of the invention are sulfides, and therefore p of Formula 1
27 is preferably zero.

28 The R_1 groups are preferably H or CH_3 , and the preferred R_2

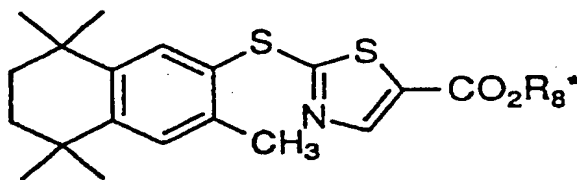
1 group on the aromatic portion of the condensed ring moiety is H, lower
2 alkyl, F or CF₃, even more preferably H or CH₃. The R₃ group is
3 preferably hydrogen; in other words the non-aromatic portion of the
4 condensed ring moiety is preferably substituted only by the R₁ groups.

5 The A-B group of the preferred compounds is (CH₂)_n-COOH or
6 (CH₂)_n-COOR₈, where n and R₈ are defined as above. Even more
7 preferably n is zero and R₈ is lower alkyl, or n is zero and B is COOH
8 or a pharmaceutically acceptable salt thereof.

9 The presently most preferred compounds of the invention are
10 shown in Table 1 with reference to Formula 4 and Formula 5.



18 Formula 4



28 Formula 5

13

TABLE 1

1	2	3	4	5	6	7
	Compound	Formula	p	Z	R ₂ [*]	R ₈ [*]
3	#					
4	1	4	0	CH	H	Et
5	2	4	0	CH	H	H
6	3	4	1	CH	H	Et
7	4	4	2	CH	H	Et
8	5	4	2	CH	H	H
9	6	4	0	CH	CH ₃	Et
10	7	4	0	CH	CH ₃	H
11	8	4	1	CH	CH ₃	Et
12	9	4	1	CH	CH ₃	H
13	10	4	2	CH	CH ₃	Et
14	11	4	2	CH	CH ₃	H
15	12	4	0	N	CH ₃	Et
16	13	4	0	N	CH ₃	H
17	14	5	0	-	-	Et
18	15	5	0	-	-	H

19

20

Modes of Administration

21

22 The compounds of this invention may be administered
 23 systemically or topically, depending on such considerations as the
 24 condition to be treated, need for site-specific treatment, quantity of
 25 drug to be administered, and numerous other considerations.

26

27 In the treatment of dermatoses, it will generally be preferred to
 28 administer the drug topically, though in certain cases such as treatment
 of severe cystic acne or psoriasis, oral administration may also be used.
 Any common topical formulation such as a solution, suspension, gel,

1 ointment, or salve and the like may be used. Preparation of such
2 topical formulations are well described in the art of pharmaceutical
3 formulations as exemplified, for example, Remington's Pharmaceutical
4 Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania.
5 For topical application, these compounds could also be administered as
6 a powder or spray, particularly in aerosol form. If the drug is to be
7 administered systemically, it may be confectioned as a powder, pill, tablet
8 or the like or as a syrup or elixir suitable for oral administration. For
9 intravenous or intraperitoneal administration, the compound will be
10 prepared as a solution or suspension capable of being administered by
11 injection. In certain cases, it may be useful to formulate these
12 compounds by injection. In certain cases, it may be useful to formulate
13 these compounds in suppository form or as extended release
14 formulation for deposit under the skin or intramuscular injection.

15 Other medicaments can be added to such topical formulation for
16 such secondary purposes as treating skin dryness; providing protection
17 against light; other medications for treating dermatoses; medicaments
18 for preventing infection, reducing irritation, inflammation and the like.

19 Treatment of dermatoses or any other indications known or
20 discovered to be susceptible to treatment by retinoic acid-like
21 compounds will be effected by administration of the therapeutically
22 effective dose of one or more compounds of the instant invention. A
23 therapeutic concentration will be that concentration which effects
24 reduction of the particular condition, or retards its expansion. In certain
25 instances, the compound potentially may be used in prophylactic
26 manner to prevent onset of a particular condition.

27 A useful therapeutic or prophylactic concentration will vary from
28 condition to condition and in certain instances may vary with the

1 severity of the condition being treated and the patient's susceptibility to
2 treatment. Accordingly, no single concentration will be uniformly
3 useful, but will require modification depending on the particularities of
4 the disease being treated. Such concentrations can be arrived at
5 through routine experimentation. However, it is anticipated that in the
6 treatment of, for example, acne, or similar dermatoses, that a
7 formulation containing between 0.01 and 1.0 milligrams per milliliter of
8 formulation will constitute a therapeutically effective concentration for
9 total application. If administered systemically, an amount between 0.01
10 and 5 mg per kg per day of body weight would be expected to effect a
11 therapeutic result in the treatment of many disease for which these
12 compounds are useful.

13 Assay of Retinoid-like Biological Activity

14 The retinoid-like activity of the compounds of the invention can
15 be confirmed in assays wherein ability of the compound to modulate
16 processes mediated by retinoid receptors, and ability of the compounds
17 to bind to retinoid receptors is measured. As it is noted in the
18 introductory section of this application for patent two main types of
19 retinoic acid receptors (RAR and RXR) exist in mammals (and other
20 organisms). Within each type there are sub-types (RAR_α, RAR_β,
21 RAR_γ, RXR_α, RXR_β and RXR_γ) the distribution of which is not
22 uniform in the various tissues and organs of mammalian organisms.
23 Moreover, specific or selective agonist-like activity on RXR receptors,
24 in preference over RAR receptors tends to result in certain beneficial
25 retinoid-like properties while avoiding certain undesirable side effects.
26 Similarly, selective agonist like activity of only one or two retinoid
27 receptor subtypes within one retinoid receptor family can also give rise
28 to beneficial pharmacological properties because of the varying

1 distribution of the sub-types in the several mammalian tissues or organs.
2 For the above-summarized reasons, agonist-like activity in any or all of
3 the retinoid receptors, as well as specific or selective activity in the
4 RXR receptor family, or selective or specific activity in any one of the
5 receptor subtypes, are all considered desirable pharmacological
6 properties.

7 In light of the foregoing the prior art has developed assay
8 procedures for testing the agonist like activity of compounds in the
9 RAR α , RAR β , RAR γ , RXR α , RXR β and RXR γ receptor subtypes. For
10 example, a chimeric receptor transactivation assay which tests for
11 agonist-like activity in the RAR α , RAR β , RAR γ , RXR α receptor
12 subtypes, and which is based on work published by Feigner P. L. and
13 Holm M. (1989) Focus, 11 2 is described in detail in U.S. Patent No.
14 5,455,265. The specification of United States Patent No. 5,455,265 is
15 expressly incorporated herein by reference.

16 A holoreceptor transactivation assay and a ligand binding assay
17 which measure the ability of the compounds of the invention to bind to
18 the several retinoid receptor subtypes, respectively, are described in
19 published PCT Application No. WO WO93/11755 (particularly on pages
20 30 - 33 and 37 - 41) published on June 24, 1993, the specification of
21 which is also incorporated herein by reference. A description of the
22 holoreceptor transactivation assay is also provided below.

23 HOLORECEPTOR TRANSACTIVATION ASSAY

24 CV1 cells (5,000 cells/well) were transfected with an RAR
25 reporter plasmid MTV-TREp-LUC (50 ng) along with one of the RAR
26 expression vectors (10 ng) in an automated 96-well format by the
27 calcium phosphate procedure of Heyman et al. Cell 68, 397 - 406. (8).
28 For RXR α and RXR γ transactivation assays, an RXR-responsive

1 reporter plasmid CRBP_{II}-tk-LUC (50 ng) along with the appropriate
2 RXR expression vectors (10 ng) was used substantially as described by
3 Heyman et al. above, and Allegretto et al. J. Biol. Chem. 268, 26625 -
4 26633. For RXR_β transactivation assays, an RXR-responsive reporter
5 plasmid CPRE-tk-LUC (50 mg) along with RXR_β expression vector (10
6 mg) was used as described in above. These reporters contain DRI
7 elements from human CRBP_{II} and certain DRI elements from
8 promoter, respectively. (see Mangelsdorf et al. The Retinoids: Biology,
9 Chemistry and Medicine, pp 319 - 349, Raven Press Ltd., New York
10 and Heyman et al., cited above) (1, 8). A β-galactosidase (50 ng)
11 expression vector was used as an internal control in the transfections to
12 normalize for variations in transfection efficiency. The cells were
13 transfected in triplicate for 6 hours, followed by incubation with
14 retinoids for 36 hours, and the extracts were assayed for luciferase and
15 β-galactosidase activities. The detailed experimental procedure for
16 holoreceptor transactivations has been described in Heyman et al.
17 above, and Allegretto et al. cited above. The results obtained in this
18 assay in connection with exemplary compounds in accordance with the
19 present invention are expressed in EC₅₀ numbers, as they are also in the
20 chimeric receptor transactivation assay. The Heyman et al. Cell 68,
21 397 - 406, Allegretto et al. J. Biol. Chem. 268, 26625 - 26633, and
22 Mangelsdorf et al. The Retinoids: Biology, Chemistry and Medicine, pp
23 319 - 349, Raven Press Ltd., New York, are expressly incorporated
24 herein by reference. The results of ligand binding assay are expressed
25 in K_d numbers. (See Cheng et al. Biochemical Pharmacology Vol. 22
26 pp 3099-3108, expressly incorporated herein by reference.)

27 Table 2 below shows the results of the holoreceptor
28 transactivation assay and Table 3 discloses the efficacy (in percentage)

1 in this assay of the test compound relative to all trans retinoic acid, for
 2 certain exemplary compounds of the invention. Table 4 shows the
 3 results of the ligand binding assay for certain exemplary compounds of
 4 the invention.

5

6

TABLE 2

7

Holoreceptor Transactivation Assay

8

Compound #

EC₅₀ (nanomolar)

9

RAR α RAR β RAR γ RXR α RXR β RXR γ

10

2

0.00

570

340

770

1600

1600

11

5

0.00

0.00

0.00

3000

0.00

2600

12

7

0.00

0.00

0.00

280

320

230

13

9

0.00

0.00

0.00

0.00

3000

1600

14

11

0.00

0.00

0.00

2800

2600

2600

15

13

0.00

0.00

0.00

54

57

42

16

15

0.00

0.00

0.00

2300

1300

1900

17 O.O in Table 2 indicates that the compound is less than 20 % as active
 18 (efficacious) in this assay than all trans retinoic acid.

19

20

TABLE 3

21

Transactivation Assay Efficacy (% of RA activity)

22

Compound #

23

RAR α RAR β RAR γ RXR α RXR β RXR γ

24

2

3

66

37

51

80

75

25

5

10

4

0

32

11

26

26

7

3

4

11

81

114

67

27

9

5

4

3

17

29

28

28

11

2

6

0

55

52

45

29

13

1

4

0

91

100

85

30

15

1

0

7

85

117

70

TABLE 4

Ligand Binding Assay

Compound #	K _d (nanomolar)					
	RAR α	RAR β	RAR γ	RXR α	RXR β	RXR γ
2	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³
5	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³
7	>10 ³	>10 ³	>10 ³	296	302	304
9	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³
11	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³
13	>10 ⁴	>10 ⁴	>10 ⁴	32	57	73
15	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³	>10 ³

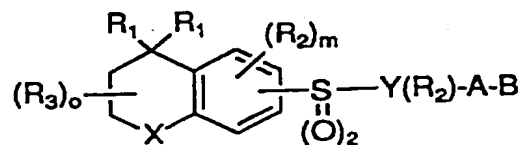
As it can be seen from the test results summarized in Tables 2, 3 and 4, the therein indicated exemplary compounds of the invention are substantially inactive as RAR agonists but are active agonists of all or some of the RXR receptor subtypes.

SPECIFIC EMBODIMENTS

The compounds of this invention can be made by the synthetic chemical pathways illustrated here. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by Formula 1.

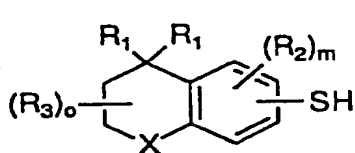
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

Homologs and
Derivatives



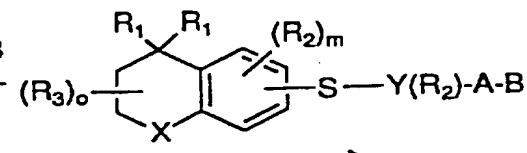
Formula 8

MCPBA
 CH_2Cl_2



Formula 2

$X_1-Y(R_2)A-B$
Formula 3
NaH, CuI

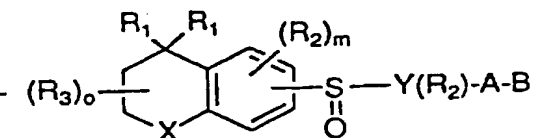


Formula 6

Homologs and
Derivatives

$NaIO_4$
dioxane

Homologs and
Derivatives



Formula 7

Reaction Scheme 1

1 In accordance with Reaction Scheme 1, a condensed cyclic thiol
2 compound of Formula 2 which is appropriately substituted with the R_1 ,
3 R_2 and R_3 groups (as these are defined in connection with Formula 1)
4 serves as the starting material. The thiol compound of Formula 2 is
5 reacted in the presence of strong base, such as sodium hydride, in a
6 polar aprotic solvent, such as dimethylformamide or
7 hexamethylphosphoramide, and a catalyst, such as copper iodide (CuI),
8 with a reagent of Formula 3 where X_1 is halogen and Y, R_4 , A and B
9 are defined as in connection with Formula 1. The reagent of Formula
10 3 is, generally speaking, available in accordance with the chemical
11 scientific or patent literature. In the presently preferred compounds of
12 the invention the A group is $(CH_2)_q$ and B is COOH or an ester or
13 amide thereof ($COOR_8$ or $CONR_9R_{10}$) and even more preferably q is
14 zero. The presently preferred reagents in accordance with Formula 3
15 used for preparation of compounds of the invention have the structure
16 $X_1-Y(R_4)-COOR_8$, and preferred examples are ethyl 4-iodobenzoate
17 (available commercially from Lancaster Chemical Co.),
18 ethyl-2-iodonicotinate and ethyl 2-iodo-5-thiazolecarboxylate. The
19 preparations of ethyl-2-iodonicotinate and of ethyl
20 2-iodo-5-thiazolecarboxylate are described below in the experimental
21 section.

22 The thiol reagent of Formula 2 is, generally speaking, also
23 available in accordance with the chemical scientific and patent
24 literature. In one group of preferred compounds of the invention the X
25 group is $[C(R_1)_2]_n$ where n is 1 (tetrahydronaphthalene derivatives) and
26 an example of the starting material for several preferred
27 tetrahydronaphthalene derivatives of the invention is

1 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthiol. The latter
2 compound is available as a result of chlorosulfonylation followed by
3 lithium aluminum hydride reduction of
4 5,6,7,8-tetrahydro-5,5,8,8-tetramethylhaphthalene in accordance with the
5 procedure of Janssen et al. (BASF A.-G.): Diphenylheteroalkylderivate,
6 ihre Herstellung und daraus hergestellte Arzneimittel und Kosmetika,
7 European Patent Application EP 0 386 452 A1 (September 12, 1990),
8 incorporated herein by reference. The above-mentioned
9 chlorosulfonylation reaction followed by lithium aluminum hydride
10 reduction to provide a thiol compound in the scope of Formula 2 is,
11 generally speaking, applicable for preparing the starting materials (i. e.
12 compounds of Formula 2) for the synthesis of the compounds of the
13 present invention.
14 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene thiol is
15 described in Chemical Abstracts 111:97241 and in French patent FR
16 2614618 A1, 11-04-1988, incorporated herein by reference.
17 Chroman-6-thiol is described in Chemical Abstracts 101:8709 and in
18 German patent DE 3314467 A1, 01-19-1984, incorporated herein by
19 reference. 2,2-Dimethylchroman-6-thiol is described in Chemical
20 Abstracts 117:48593 and in Japanese patent JP 03232882 A2
21 10-16-1991, incorporated herein by reference.

22 In addition to the availability of the thiol compounds of Formula
23 2 from the foregoing and other scientific publications and patent
24 description (through the above-mentioned chlorosulfonation reaction
25 followed by reduction with LiAlH_4) the thiol compounds can also be
26 prepared from bromo substituted tetrahydronaphthalene, chroman,
27 thiochroman and tetrahydroquinoline compounds which are known or
28 available in the art. For example, United States Patent Nos. 5,278,318,

1 5,348,972, 5,407,937, and 5,407,937 describe 2-alkyl and/or 4-alkyl
2 substituted thiochromans also substituted with a bromo group in the 6
3 position. United States Patent No. 5,346,585 describes 2-alkyl and/or
4 4-alkyl substituted thiochromans substituted with a bromo group in the
5 7 position. United States Patent Nos. 5,324,744, 5,348,975 and
6 5,346,585 describe 2-alkyl and/or 4-alkyl substituted chromans
7 substituted with a bromo group in the 7 position. United States Patent
8 No. 5,348,972 describes 4-alkyl substituted tetrahydroquinoline
9 compounds substituted with a bromo group in the 6 position. The
10 specifications of United States Patent Nos. 5,278,318, 5,324,744,
11 5,346,585, 5,348,972, 5,348,975, and 5,407,937 are expressly incorporated
12 herein by reference. These and analogous bromo compounds can be
13 reacted with 2 equivalents of *t*-butyl lithium in an inert ether-type
14 solvent, and the resulting anion formed after lithium halogen exchange
15 is quenched with sulfur to provide the thiol compounds of **Formula 2**.

16 Referring back again to **Reaction Scheme 1** the reaction between
17 the thiol compounds of **Formula 2** and the aromatic or heteroaromatic
18 halogenated compounds of **Formula 3** gives rise to the disubstituted
19 sulfide compounds of **Formula 6**. The disubstituted sulfide compounds
20 of **Formula 6** are within the scope of the present invention and
21 represent a class of preferred compounds of the invention, where with
22 reference to **Formula 1**, *p* is zero. The compounds of **Formula 6** are
23 oxidized to provide the sulfoxide compounds of **Formula 7** which are
24 also within the scope of the invention and where, with reference to
25 **Formula 1**, *p* is 1. The oxidation to the sulfoxide stage is conducted
26 with a suitable oxidizing agent, such as sodium periodate (NaIO₄) in an
27 ether like solvent, such as dioxane. The disubstituted sulfide
28 compounds of **Formula 6** are also oxidized in accordance with **Reaction**

1 Scheme 1 to the sulfone compounds of Formula 8, which are also
2 within the scope of the present invention. In these compounds, with
3 reference to Formula 1, p is 2. Oxidation to the sulfone stage is carried
4 out by reaction with a strong oxidizing agent, such as
5 m-chloroperoxybenzoic acid in an aprotic solvent, preferably methylene
6 chloride. In the situations where the X group of Formula 1 is sulfur
7 (thiochroman derivatives), the above-described oxidation reactions may
8 also oxidize the ring sulfur to the sulfoxide and/or sulfone stage,
9 respectively.

10 In addition to the above described oxidation reactions the
11 compounds of Formulas 6, 7 and 8 can be subjected to such further
12 transformations, primarily affecting the A-B group, which are per se
13 well known in the art, and which result in still further compounds
14 within the scope of Formula 1. Reactions frequently carried out which
15 affect the B group typically are saponification of an ester group,
16 esterification of a carboxylic acid, formation of an amide or
17 homologation of an acid or ester. These reactions are indicated in
18 Reaction Scheme 1 by conversion to "homologs and derivatives".
19 Regarding these reactions and also regarding the synthesis of
20 halogenated compounds of Formula 3 suitable for the coupling
21 reactions described in Reaction Scheme 1 (where such compound is not
22 available commercially or from a known literature procedure) the
23 following general synthetic methodology is noted.

24 Carboxylic acids are typically esterified by refluxing the acid in a
25 solution of the appropriate alcohol in the presence of an acid catalyst
26 such as hydrogen chloride or thionyl chloride. Alternatively, the
27 carboxylic acid can be condensed with the appropriate alcohol in the
28 presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The

1 ester is recovered and purified by conventional means. Acetals and
2 ketals are readily made by the method described in March, "Advanced
3 Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810).
4 Alcohols, aldehydes and ketones all may be protected by forming
5 respectively, ethers and esters, acetals or ketals by known methods such
6 as those described in McOmie, Plenum Publishing Press, 1973 and
7 Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

8 A means for making compounds where A is $(CH_2)_q$ (q is 1 - 5) is
9 to subject the compounds of Formula 1, where B is an acid or other
10 function, to homologation, using the well known Arndt-Eistert method
11 of homologation, or other known homologation procedures. Similar
12 homologations (and several of the other herein mentioned synthetic
13 transformations) can be transformed on the reagent $X_1-Y(R_2)-A-B$.
14 Compounds of the invention, where A is an alkenyl group having one or
15 more double bonds can be made, for example, by having the requisite
16 number of double bonds incorporated into the reagent $X_1-Y(R_2)-A-B$.
17 Generally speaking, such compounds where A is an unsaturated carbon
18 chain can be obtained by synthetic schemes well known to the
19 practicing organic chemist; for example by Wittig and like reactions, or
20 by introduction of a double bond by elimination of halogen from an
21 alpha-halo-carboxylic acid, ester or like carboxaldehyde. Compounds of
22 the invention where the A group has a triple (acetylenic) bond can be
23 made by using the corresponding aryl or heteroaryl aldehyde
24 intermediate. Such intermediate can be obtained by reactions well
25 known in the art, for example, by reaction of a corresponding methyl
26 ketone with strong base, such as lithium diisopropylamide.

27 The acids and salts derived from compounds of Formula 1 are
28 readily obtainable from the corresponding esters. Basic saponification

1 with an alkali metal base will provide the acid. For example, an ester
2 of Formula 1 may be dissolved in a polar solvent such as an alkanol,
3 preferably under an inert atmosphere at room temperature, with about
4 a three molar excess of base, for example, potassium or lithium
5 hydroxide. The solution is stirred for an extended period of time,
6 between 15 and 20 hours, cooled, acidified and the hydrolysate
7 recovered by conventional means.

8 The amide may be formed by any appropriate amidation means
9 known in the art from the corresponding esters or carboxylic acids.
10 One way to prepare such compounds is to convert an acid to an acid
11 chloride and then treat that compound with ammonium hydroxide or an
12 appropriate amine.

13 Alcohols are made by converting the corresponding acids to the
14 acid chloride with thionyl chloride or other means (J. March,
15 "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book
16 Company), then reducing the acid chloride with sodium borohydride
17 (March, Ibid, pg. 1124), which gives the corresponding alcohols.
18 Alternatively, esters may be reduced with lithium aluminum hydride at
19 reduced temperatures. Alkylating these alcohols with appropriate alky
20 halides under Williamson reaction conditions (March, Ibid, pg. 357)
21 gives the corresponding ethers. These alcohols can be converted to
22 esters by reacting them with appropriate acids in the presence of acid
23 catalysts or dicyclohexylcarbodiimide and dimethylaminopyridine.

24 Aldehydes can be prepared from the corresponding primary
25 alcohols using mild oxidizing agents such as pyridinium dichromate in
26 methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or
27 dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K.,
28 Swern, D., Tetrahedron, 1978, 34, 1651).

1 Ketones can be prepared from an appropriate aldehyde by
2 treating the aldehyde with an alkyl Grignard reagent or similar reagent
3 followed by oxidation.

4 Acetals or ketals can be prepared from the corresponding
5 aldehyde or ketone by the method described in March, Ibid, p 810.

6 Compounds of Formula 1 where B is H can be prepared from
7 the corresponding halogenated aromatic compounds, preferably where
8 the halogen is I.

9 Specific Examples

10 6-Iodonicotinic acid

11 To 27.97 g (186.6 mmol) of sodium iodide cooled to -78°C was
12 added 121.77 g (71.6 ml, 952.0 mmol) of hydroiodic acid (57 wt %).
13 The reaction mixture was allowed to warm slightly with stirring for 5
14 minutes, and then 30.00 g (190.4 mmol) of 6-chloronicotinic acid was
15 added. The resulting mixture was allowed to warm to room
16 temperature with stirring and then heated at 120-125°C in an oil bath
17 for 42 hours. A dark brown layer formed above the yellow solid
18 material. The reaction mixture was allowed to cool to room
19 temperature and then poured into acetone (chilled to 0°C). The
20 resultant yellow solid was collected by filtration, washed with 200 ml of
21 1N NaHSO₃ solution, and dried in high vacuum (3 mm Hg) to give the
22 title compound as a pale yellow solid.
23 PMR (DMSO-d₆): δ 7.90 (1H, dd, J = 8.1, 2 Hz), 7.99 (1H, d, J = 8.1
24 Hz), 8.80 (1H, d, J = 2.Hz).

25 Ethyl 6-iodonicotinate

26 To a suspension of 23.38 g (94.2 mmol) of 6-iodonicotinic acid in
27 100 ml of dichloromethane was added a solution of 19.86 g (103.6
28 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

1 in 250 ml of dichloromethane. To this suspension was added 12.40 g
2 (15.8 ml, 269.3 mmol) of ethanol (95%) and 1.15 g (9.4 mmol) of
3 4-dimethylaminopyridine. The resulting solution mixture was then
4 heated at 50°C in an oil bath for 24.5 hours, concentrated in vacuo,
5 partitioned between 200 ml of water and 250 ml of ethyl ether, and the
6 layers were separated. The aqueous phase was washed with 2 x 150
7 ml-portions of ethyl ether. All organic phases were combined, washed
8 once with 75 ml of brine solution, dried over MgSO_4 , filtered and
9 concentrated in vacuo to a yellow solid. Purification by flash
10 chromatography (silica, 10% ethyl acetate in hexane) yielded the title
11 compound as a white solid.
12 PMR (CDCl_3): δ 1.41 (3H, t, $J = 7.1$ Hz), 4.41 (2H, q, $J = 7.1$ Hz),
13 7.85 (1H, d, $J = 8.2$ Hz), 7.91 (1H, dd, $J = 8.2, 2.1$ Hz), 8.94 (1H, d, J
14 $= 2.1$ Hz).

15 Ethyl 2-iodo-5-thiazolecarboxylate

16 To a solution of 4.96 g (31.5 mmol) of 2-trimethylsilylthiazole in
17 100 ml of ether stirring at -78 °C under argon, was dropwise added
18 n-BuLi (23.0 mL, 36.8 mmol, 1.6 M in hexanes) and the resulting
19 mixture stirred at -78 °C for 30 min. Ethyl chloroformate (7.60 mL,
20 10.6 g, 98 mmol) was added and the reaction stirred at -78 °C for 30
21 min and at room temperature for 30 min. The solution was then
22 recooled to -78 °C where a solution of 10.75 g (42.5 mmol) of I_2 in 50
23 mL of tetrahydrofuran was cannulated into the cool solution. The
24 reaction was warmed slowly to room temperature and stirred for 15 h.
25 The reaction was then cooled to -78 °C, quenched with water and
26 sodium thiosulfate, and extracted with diethyl ether (3x). The organic
27 layers were combined, washed with brine, dried (Na_2SO_4), filtered, and
28 the solvents removed in-vacuo. The crude product was purified by

1 flash chromatography on silica gel (85:15/hexane:ethyl acetate) to give
2 the title compound as an oil (0.89 g, 10%):

3 ¹H NMR (300 MHz, CDCl₃) δ 1.38 (t, 3H, J = 7.1 Hz), 4.36 (q, 2H, J =
4 7.1 Hz), 8.11 (s, 1H).

5 Ethyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate
6 (Compound 1)

7 Sodium hydride (0.807 g, 60% dispersion in oil, 21 mmol) was
8 rinsed 3x with hexane and dried under vacuum. The vacuum was
9 broken with dry argon and to this was added 10.0 mL of
10 dimethylformamide and the mixture cooled to 0 °C.
11 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthylthiol available in
12 accordance with Janssen et al. European Patent Application EP 0 386
13 452 A1, September 12, 1990, (702 mg, 3.2 mmol) was then added and
14 the resulting mixture stirred at 0-10 °C for 1.25 h. Copper (I) iodide
15 (0.592 g, 3.1 mmol) was added, the mixture stirred at 0 °C for 45 min
16 and a solution of ethyl 4-iodobenzoate (0.839 g, 3.04 mmol) in 2.0 ml of
17 dimethylformamide was added. The mixture was heated to 75 °C for 48
18 h, the bath removed, and stirred at room temperature for 48 h. The
19 reaction was then poured onto ice and extracted with ether (4x), the
20 organic layers were combined, washed with brine, dried (MgSO₄),
21 filtered, and the solvents removed in-vacuo to give an orange solid.
22 The crude product was purified by flash chromatography on silica gel
23 (98:2/hexane:ethyl acetate) to give the title compound as a clear oil
24 (0.32 g, 27%):

25 ¹H NMR (300 MHz, CDCl₃) δ 1.26 (s, 6H), 1.30 (s, 6H), 1.37 (t, 3H, J =
26 7.1 Hz), 1.70 (s, 4H), 4.34 (q, 2H, J = 7.1 Hz), 7.17 (d, 2H J = 8.5 Hz),
27 7.22 (dd, 1H, J = 2.0, 8.2 Hz), 7.32 (d, 1H, J = 8.2 Hz), 7.44 (d, 1H, J
28 = 2.0 Hz), 7.89 (d, 2H J = 8.5 Hz).

1 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoic acid

2 (Compound 2)

3 To a solution of 70 mg (0.19 mmol) of ethyl
4 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoate
5 (Compound 1) in 4.0 mL of tetrahydrofuran was added 1.0 mL of
6 LiOH (1.9 N aqueous solution) and 1.5 mL of MeOH. The solution
7 was heated at 55 °C for 3 h, cooled to room temperature and
8 concentrated in vacuo. The residue was diluted with water and
9 extracted with hexane. The aqueous layer was acidified to pH=1 using
10 10% HCl and extracted twice with diethyl ether. The combined organic
11 layers were washed with brine, dried (MgSO₄), filtered and the solvents
12 removed in vacuo. Purification of crude product by flash
13 chromatography on silica gel (7:3/hexane:ethyl acetate) gave the title
14 compound as a white solid (40 mg, 62%):

15 ¹H NMR (300 MHz, CDCl₃) δ 1.27 (s, 6H), 1.31 (s, 6H), 1.71 (s, 4H),
16 7.18 (d, 2H J = 8.6 Hz), 7.25 (dd, 1H, J = 2.0, 8.2 Hz), 7.34 (d, 1H, J
17 = 8.2 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.95 (d, 2H J = 8.6 Hz).

18 Ethyl

19 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfoxy)benzoate

20 (Compound 3)

21 To a solution of ethyl
22 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate
23 (Compound 1, 0.18 g, 0.31 mmol) in 4 ml of dioxane was dropwise
24 added a solution of sodium periodate (0.181 g, 0.85 mmol) in 1.7 mL
25 H₂O and 4.0 mL of MeOH. The resulting mixture was stirred at 50 °C
26 for 120 h. The reaction was then cooled to room temperature, brine
27 was added and the mixture extracted using ether (2x). The combined
28 organic layers were then dried (MgSO₄), filtered and concentrated to

1 give a clear oil. Purification by flash chromatography
2 (85:15/hexane:ethyl acetate) gave the title compound as a clear oil (57
3 mg, 30%):
4 ¹H NMR (300 MHz, CDCl₃) δ 1.24 (s, 6H), 1.26 (s, 3H), 1.28 (s, 3H),
5 1.39 (t, 3H, J = 7.1 Hz), 1.67 (s, 4H), 4.38 (q, 2H, J = 7.1 Hz), 7.27
6 (dd, 1H, J = 1.9, 8.3 Hz), 7.36 (d, 1H J = 8.3 Hz), 7.64 (d, 1H, J = 1.9
7 Hz), 7.72 (d, 2H, J = 8.4 Hz), 8.14 (d, 2H J = 8.4 Hz).

8 Ethyl

9 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate
10 (Compound 4)

11 To a solution of 230 mg (0.63 mmol) of ethyl
12 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate
13 (Compound 1) in 5.0 mL of methylene chloride was added
14 m-chloroperoxybenzoic acid (200 mg, 0.60 mmol, 50-60%) and the
15 resulting solution stirred at room temperature for 24 h. The reaction
16 mixture was diluted with water and extracted with methylene chloride
17 (2x). The combined organic layers were dried (MgSO₄), filtered, and
18 the solvents were removed in vacuo to give a white solid. The crude
19 product was purified by flash chromatography on silica gel
20 (96:4/hexane:ethyl acetate) to give the title compound as a white solid
21 (0.11 g, 87%):

22 ¹H NMR (300 MHz, CDCl₃) δ 1.25 (s, 6H), 1.29 (s, 6H), 1.39 (t, 3H, J =
23 7.1 Hz), 1.68 (s, 4H), 4.39 (q, 2H, J = 7.1 Hz), 7.42 (d, 2H J = 8.4 Hz),
24 7.61 (dd, 1H, J = 2.1, 8.4 Hz), 7.90 (d, 1H, J = 2.1 Hz), 8.00 (d, 2H J
25 = 8.5 Hz), 8.15 (d, 2H J = 8.5 Hz).

26 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoic acid
27 (Compound 5)

28 To a solution of 95 mg (0.23 mmol) of ethyl

1 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate
2 (Compound 4) in 4.0 mL of tetrahydrofuran was added 1.0 mL of
3 LiOH (2.6 N aqueous solution) and 1.4 mL of MeOH. The solution
4 was heated at 55 °C for 2.5 h, cooled to room temperature and
5 concentrated in vacuo. The residue was diluted with brine, acidified to
6 pH = 1 using 10% HCl and extracted with ether (2x). The combined
7 organic layers were washed with brine, dried (MgSO₄), filtered and the
8 solvents were removed in vacuo to give the title compound as a white
9 solid (80 mg, 91%):

10 ¹H NMR (300 MHz, CDCl₃) δ 1.26 (s, 6H), 1.29 (s, 6H), 1.68 (s, 4H),
11 7.17 (d, 2H J = 8.5 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.63 (dd, 1H, J =
12 2.1, 8.4 Hz), 7.92 (d, 1H, J = 2.1 Hz), 8.04 (d, 2H J = 8.5 Hz), 8.22 (d,
13 2H J = 8.5 Hz).

14 Ethyl

15 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate

16 (Compound 6)

17 Sodium hydride (65 mg, 60 % dispersion in oil, 1.62 mmol) was
18 rinsed 3x with hexane and dried under vacuum. The vacuum was
19 broken with dry argon and 2.5 mL of hexamethylphosphoramide
20 (HMPA) and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol
21 (see Janssen et al. European Patent Application EP 0 386 452 A1)
22 (0.38 g, 1.62 mmol) were added sequentially. After 30 min at 50 °C,
23 copper (I) iodide (257 mg, 1.35 mmol) was added, which caused the
24 solution to become deep green. The solution was stirred for 15 min
25 and ethyl 4-iodobenzoate (373 mg, 1.35 mmol) was added. The
26 solution was heated to 90 °C for 5 h, the bath removed, and stirring
27 continued overnight at room temperature. Water was added and the
28 products extracted with diethyl ether (3x). The combined ether layers

1 were washed with brine, dried (MgSO_4), filtered and the solvents
2 removed in vacuo. The residue was purified by flash chromatography
3 on silica gel (95:5/hexane:ethyl acetate) to give the title compound as a
4 light yellow solid (260 mg, 50 %):

5 ^1H NMR (300 MHz, CDCl_3): δ 1.24 (s, 6H), 1.30 (s, 6H), 1.36 (t, 3H, J =
6 7.1 Hz), 1.69 (s, 4H), 2.28 (s, 3H), 4.33 (q, 2H, J = 7.1 Hz), 7.05 (d,
7 2H, J = 8.6 Hz), 7.23 (s, 1H), 7.26 (s, 1H), 8.87 (d, 2H, J = 8.6 Hz)
8 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoic acid
9 (Compound 7)

10 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-
11 2-naphthylthio)benzoate (Compound 6, 170 mg, 0.44 mmol) was
12 dissolved in ethyl alcohol (4 mL) and the solution treated with 2N
13 aqueous KOH (2 mL). The solution was heated to 50 °C for 4 h and
14 concentrated in vacuo. The residue was treated with diethyl ether,
15 cooled to 0 °C, and acidified with 10% aqueous HCl. The product was
16 extracted with diethyl ether, washed with water, brine, dried (MgSO_4),
17 filtered and the solvents were removed under reduced pressure to give
18 the title compound as a yellow solid (158 mg, 100 %):

19 ^1H NMR (300 MHz, CDCl_3): δ 1.25 (s, 6H), 1.31 (s, 6H), 1.69 (s, 4H),
20 2.29 (s, 3H), 7.05 (d, 2H, J = 8.5 Hz), 7.25 (s, 1H), 7.26 (s, 1H), 7.92 (d,
21 2H, J = 8.5 Hz)

22 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)-
23 benzoate (Compound 8)

24 To a solution of ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-
25 pentamethyl-2-naphthylthio)benzoate (Compound 6, 0.12 g, 0.31 mmol)
26 in 4 mL of dioxane was dropwise added 1.0 mL of 0.42M sodium
27 periodate (0.42 mmol, 180 mg in 1.3 mL H_2O and 0.7 mL of MeOH).
28 An additional 6.0 mL of methanol was added and the resulting mixture

1 was stirred at room temperature for 42 h. The reaction was then
2 heated at 50 °C for 200 h. Additional sodium periodate (80 mg, 0.38
3 mmol) and 2.0 mL of dioxane was added during this time. The reaction
4 was then cooled to room temperature, brine was added and the mixture
5 extracted using ether (2x). The organic layers were then dried
6 (MgSO₄), filtered and concentrated to give a clear oil. Purification by
7 flash chromatography (85:15/hexane:ethyl acetate) gave the title
8 compound as a clear oil (65 mg, 52%):

9 ¹H NMR (300 MHz, CDCl₃) δ 1.23 (s, 3H), 1.24 (s, 3H), 1.26 (s, 3H),
10 1.30 (s, 3H), 1.39 (t, 3H, J = 7.1 Hz), 1.67 (s, 4H), 2.31 (s, 3H), 4.38 (q,
11 2H, J = 7.1 Hz), 7.08 (s, 1H), 7.66 (d, 2H J = 8.4 Hz), 7.76 (s, 1H),
12 8.12 (d, 2H J = 8.4 Hz).

13 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)benzoic
14 acid (Compound 9)

15 To a solution of 58 mg (0.15 mmol) of ethyl
16 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)benzoate
17 (Compound 8) in 4.0 mL of tetrahydrofuran was added 1.0 mL of
18 LiOH (2N aqueous solution) and 2.0 mL of MeOH. The solution was
19 heated at 55 °C for 2 h and stirred at room temperature for 8 h. The
20 reaction mixture was then concentrated in vacuo. The residue was
21 diluted with brine and 10 % HCl and extracted with diethyl ether (2x).
22 The combined ether layers were dried (MgSO₄), filtered, and the
23 solvents removed in vacuo to give the title compound as a white solid
24 (0.39 mg, 72%):

25 ¹H NMR (300 MHz, CDCl₃) δ 1.22 (s, 3H), 1.24 (s, 3H), 1.26 (s, 3H),
26 1.29 (s, 3H), 1.66 (s, 4H), 2.34 (s, 3H), 7.10 (s, 1H), 7.70 (d, 2H J = 8.3
27 Hz), 7.76 (s, 1H), 8.17 (d, 2H, J = 8.3 Hz).

28 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)-

1 benzoate (Compound 10)

2 To a solution of 69 mg (0.18 mmol) of ethyl
3 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate
4 (Compound 6) in 2.0 mL of methylene chloride was dropwise added a
5 solution of 87 mg of m-chloroperoxybenzoic acid (0.27 mmol, 50-60%)
6 in 2.0 mL of methylene chloride, and the resulting solution was stirred
7 for 3 h. The reaction was diluted with water and extracted with
8 methylene chloride (2x). The combined organic layers were dried
9 (MgSO₄), filtered, and the solvents removed in vacuo to give a white
10 solid. The crude product was purified by flash chromatography on
11 silica gel (9:1/hexane:ethyl acetate) to give the title compound as a
12 white solid (51 mg, 94%):

13 ¹H NMR (300 MHz, CDCl₃) δ 1.25 (s, 6H), 1.34 (s, 6H), 1.39 (t, 3H, J =
14 7.1 Hz), 1.70 (s, 4H), 2.33 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 7.11 (s,
15 1H), 7.90 (d, 2H J = 8.5 Hz), 8.15 (s & d overlapping, 3H).

16 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoic
17 acid (Compound 11)

18 To a solution of 50 mg (0.12 mmol) of ethyl
19 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoate
20 (Compound 10) in 3.0 mL of tetrahydrofuran was added 1.0 mL of
21 LiOH (1N aqueous solution). The solution was heated at 50 °C for 3 h,
22 cooled to room temperature and concentrated in vacuo. The residue
23 was diluted with brine, acidified using 10% HCl and extracted with
24 ether (2x). The combined ether layers were dried (MgSO₄), filtered,
25 and the solvents were removed in vacuo to give the title compound as
26 a white solid (45 mg, 98%):

27 ¹H NMR (300 MHz, CDCl₃) δ 1.25 (s, 6H), 1.34 (s, 6H), 1.70 (s, 4H),
28 2.33 (s, 3H), 7.12 (s, 1H), 7.95 (d, 2H J = 8.4 Hz), 8.15 (s, 1H), 8.22 (d,

1 2H, $J = 8.4$ Hz).

2 Ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-
3 nicotinate (Compound 12)

4 Sodium hydride (171 mg, 60 % dispersion in oil, 4.3 mmol) was
5 rinsed 3 x with hexane and dried under vacuum. The vacuum was
6 broken with dry argon and 6.6 mL of hexamethylphosphoramide
7 (HMPA) and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol
8 (1.0 g, 4.27 mmol) were added sequentially. After 30 min at 50 °C,
9 copper (I) iodide (678 mg, 3.56 mmol) was added, which caused the
10 solution to become deep green. The solution was stirred for 15 min
11 and ethyl 2-iodonicotinate (986 mg, 3.56 mmol) was added. The
12 solution was heated to 90 °C for 5 h, the bath was removed, and stirring
13 was continued overnight at room temperature. Water was added and
14 the products were extracted with diethyl ether (3x). The combined
15 ether layers were washed with brine, dried (MgSO_4), filtered and the
16 solvents removed in vacuo. The residue was purified by flash
17 chromatography on silica gel (95:5/hexane:ethyl acetate) to give the title
18 compound as a light yellow solid (642 mg, 47 %):

19 $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.26 (s, 6H), 1.31 (s, 6H), 1.37 (t, 3H, $J =$
20 7.1 Hz), 1.69 (s, 4H), 2.32 (s, 3H), 4.36 (q, 2H, $J = 7.1$ Hz), 6.68 (d,
21 1H, $J = 8.0$ Hz), 7.73 (s, 1H), 7.53 (s, 1H), 7.99 (dd, 1H, $J = 2.3, 8.0$
22 Hz), 9.00 (d, 1H, $J = 2.3$ Hz)

23 2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinic acid
24 (Compound 13)

25 To a solution of ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-
26 2-naphthylthio)nicotinate (Compound 12, 300 mg, 0.78 mmol) and
27 ethanol (8 mL) was added 2N KOH (2 mL) and the resulting solution
28 stirred at 50 °C for 34 h. The solution was concentrated in vacuo,

1 water added, and the mixture was acidified with 10% aqueous HCl.

2 The product was extracted with methylene chloride (3X) and the

3 combined organic extracts were washed with brine, dried (MgSO₄),

4 filtered and concentrated in vacuo. The solid residue was recrystallized

5 from acetonitrile/methanol (4:1) to give the title compound (233 mg,

6 84%) as light yellow crystals:

7 ¹H NMR (300 MHz, CDCl₃) δ 1.21 (s, 6H), 1.26 (s, 6H), 1.63 (s, 4H),

8 2.23 (s, 3H), 6.81 (d, 1H, J = 8.2 Hz), 7.39 (s, 1H), 7.50 (s, 1H), 7.05

9 (dd, 1H, J = 2.1, 8.2 Hz), 8.84 (d, 1H, J = 2.1 Hz)

10 Ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl

11 -2-naphthylthio)-5-thiazolecarboxylate (Compound 14)

12 Sodium hydride (0.057 g, 60% dispersion in oil, 2.4 mmol) was

13 rinsed 3 x with hexane and dried under vacuum. The vacuum was

14 broken and dry argon was added. To this was added 5.0 mL of

15 hexamethylphosphoramide.

16 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol (445 mg, 1.9

17 mmol) was then added and the resulting mixture heated at 50 °C for 45

18 min. Copper (I) iodide (0.36 g, 1.9 mmol) was added and the mixture

19 heated at 55 °C for 1.5 h and a solution of ethyl

20 2-iodo-5-thiazolecarboxylate (0.65 g, 2.3 mmol) in 2.0 ml of

21 hexamethylphosphoramide was added. The mixture was heated to 95 °C

22 for 2 h. The reaction was then cooled to 0 °C, quenched with water,

23 and extracted with diethyl ether (2x). The organic layers were

24 combined, washed with brine, dried (MgSO₄), filtered, and the solvents

25 were removed in vacuo. The crude product was purified by flash

26 chromatography on silica gel (85:15/hexane:ethyl acetate) to give the

27 title compound as an orange oil (0.30 g, 41%)

28 ¹H NMR (300 MHz, CDCl₃) δ 1.28 (s, 6H), 1.32 (s, 6H), 1.32 (t, 3H, J =

1 7.1 Hz), 1.70 (s, 4H), 2.41 (s, 3H), 4.29 (q, 2H, J = 7.1 Hz), 7.30 (s, 1H
2), 7.60 (s, 1H), 8.19 (s, 1H).

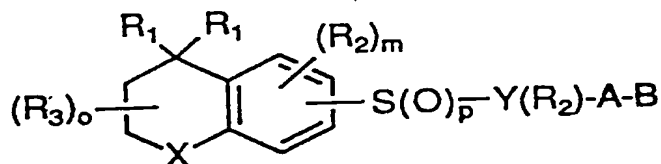
3 2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-5-thiazolecar
4 boxylic acid (Compound 15)

5 To a solution of 0.183 g (0.47 mmol) of ethyl
6 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
7 naphthylthio)-5-thiazolecarboxylate (Compound 14) in 2.0 mL of THF
8 was added 1.0 mL of LiOH (2.1 N aqueous solution) and 1.0 mL of
9 MeOH. The solution was heated at 50 °C for 1 h, cooled to room
10 temperature and concentrated in vacuo. The residue was diluted with
11 water, the aqueous layer acidified to pH=1 using 10% HCl and
12 extracted with ether. The combined organic layers were washed with
13 brine, dried (MgSO₄), filtered, and the solvents removed in vacuo to
14 give the title compound as a white solid (131 mg, 78%):
15 ¹H NMR (300 MHz, CD₃OD) δ 1.28 (s, 6H), 1.32 (s, 6H), 1.73 (s, 4H),
16 2.40 (s, 3H), 7.42 (s, 1H), 7.63 (s, 1H), 8.12 (s, 1H).

17

1 WHAT IS CLAIMED IS:

2 1. A compound of the formula



11 wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons,

12 or

13 X is [C(R₁)₂]_n where n is an integer between 0 and 2;14 R₁ is independently H or alkyl of 1 to 6 carbons;15 R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro
16 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or
17 alkylthio of 1 to 6 carbons;18 R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

19 m is an integer having the value of 0 - 3;

20 o is an integer having the value of 0 - 4;

21 p is an integer having the value of 0 - 2;

22 Y is a phenyl or naphthyl group, or heteroaryl selected from a
23 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,
24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrololyl, said phenyl and
25 heteroaryl groups being optionally substituted with one or two R₂
26 groups;27 A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6

1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds,
2 and

3 B is hydrogen, COOH or a pharmaceutically acceptable salt
4 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO,
5 CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower
6 alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1
7 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or
8 (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a
9 cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower
10 alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1
11 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower
12 alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower
13 alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.

14 2. A compound in accordance with Claim 1 wherein X is
15 [C(R₁)₂]_n and n is 1.

16 3. A compound in accordance with Claim 1 wherein X is S.

17 4. A compound in accordance with Claim 1 wherein X is O.

18 5. A compound in accordance with Claim 1 wherein X is NR'.

19 6. A compound in accordance with Claim 1 wherein Y is
20 phenyl.

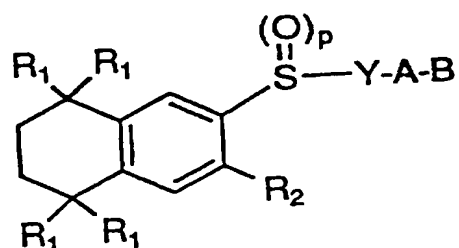
21 7. A compound in accordance with Claim 6 wherein the
22 phenyl group is 1,4 substituted.

23 8. A compound in accordance with Claim 1 wherein Y is

24 pyridyl. 9. A compound in accordance with Claim 8 wherein
25 the pyridyl group is 2,5 substituted.

26 10. A compound in accordance with Claim 1 wherein Y is
27 thiazolyl.

28 11. A compound of the formula



wherein R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, or fluoro substituted alkyl of 1 to 6 carbons;

Y is a phenyl or heteroaryl selected from a group consisting of pyridyl and thiazolyl;

p is an integer having the value of 0 - 2;

A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, and

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.

12. A compound in accordance with Claim 11 wherein the R₁ groups are methyl.

1 13. A compound in accordance with Claim 12 wherein R_2 is H
2 or CH_3 .

3 14. A compound in accordance with Claim 13 wherein A is
4 $(CH_2)_q$ where q is 0 and wherein B is COOH or a pharmaceutically
5 acceptable salt thereof, $COOR_8$, or $CONR_9R_{10}$.

6 15. A compound in accordance with Claim 14 wherein Y is
7 1,4-substituted phenyl.

8 16. A compound in accordance with Claim 15 wherein p is
9 zero.

10 17. A compound in accordance with Claim 16 which is ethyl
11 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate,
12 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoic acid, ethyl
13 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate, or
14 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoic acid.

15 18. A compound in accordance with Claim 15 wherein p is 1.

16 19. A compound in accordance with Claim 18 which is ethyl
17 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfoxy)benzoate,
18 ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsul-
19 foxy)benzoate or 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-
20 2-naphthylsulfoxy)benzoic acid.

21 20. A compound in accordance with Claim 15 wherein p is 2.

22 21. A compound in accordance with Claim 20 which is ethyl
23 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate,
24 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoic acid,
25 ethyl
26 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoate
27 or
28 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoic

1 acid.

2 22. A compound in accordance with Claim 14 wherein Y is
3 2,5-substituted pyridyl.

4 23. A compound in accordance with Claim 22 wherein p is
5 zero.

6 24. A compound in accordance with Claim 23 which is ethyl
7 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinate or
8 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinic acid.

9

10 25. A compound in accordance with Claim 14 wherein Y is
11 2-thiazolyl substituted in the 5 position with the A-B group.

12 26. A compound in accordance with Claim 25 wherein p is
13 zero.

14 27. A compound in accordance with Claim 26 which is ethyl
15 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-5-thiazolecar
16 boxylate and 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-
17 naphthylthio)-5-thiazolecarboxylic acid.

INTERNATIONAL SEARCH REPORT

International Application No
PC., US 96/17295A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C323/62 C07C317/44 C07D213/80 C07D277/56 A61K31/235
A61K31/455 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 719 043 A (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES GALDERMA) 27 October 1995 see the whole document ---	1-9, 11-24
A	US 5 272 156 A (R.A.S. CHANDRARATNA) 21 December 1993 cited in the application see column 1 - column 2 ---	1,10, 25-27
A	WO 93 06086 A (PFIZER) 1 April 1993 see page 2 - page 3 ---	1
A	US 5 248 823 A (B. JANSSEN, ET AL.) 28 September 1993 see column 1 - column 2 ---	1
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

18 February 1997

Date of mailing of the international search report

0 4. 03. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+ 31-70) 340-3016

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International Application No

PC1, JS 96/17295

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 722 928 A (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES GALDERMA) 24 July 1996 see page 2 - page 4; examples 6-8,12,13 ---	1,2
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 18, 30 August 1996, WASHINGTON, DC, US, pages 3556-3563, XP002024736 R.L. BEARD, ET AL.: "Synthesis and structure-activity relationships of retinoid X receptor selective diaryl sulphide analogues of retinoic acid" see the whole document ---	1-27
X	JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 433, 1923, WEINHEIM, DE, pages 327-350, XP002025422 H. MEYER: "Zur Kenntnis der aromatische Sulfosäure und Sulfone" see pages 347 - 350; page 350 ---	1,2,6,7, 11
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no. 24, December 1980, LETCHWORTH, GB, pages 1183-1184, XP002024785 K. TAKAKI, ET AL.: "Annellation reactions of 3-phenylthiobut-3-en-2-one. A new method of constructing fused phenols" see compound 5 ---	1,2,6,11
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 57, no. 13, 19 June 1992, WASHINGTON, DC, US, pages 3540-3545, XP002024786 A. PADWA, ET AL.: "Cycloaddition reactions of 1,3- and 2,3-bis(phenylsulphonyl) 1,3-dienes with enamines" see compound 15 ---	1,2,6,11
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 386 (M-754), 14 October 1988 & JP 63 137889 A (KANZAKI PAPER MANUFACTURING), 9 June 1988, see abstract ---	1,2,6,7, 11
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 311 (M-734), 24 August 1988 & JP 63 082778 A (KANZAKI PAPER MANUFACTURING), 13 April 1988, see abstract ---	1,2,6,11

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PC 1, US 96/17295

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PATENT ABSTRACTS OF JAPAN vol. 011, no. 133 (C-418), 25 April 1987 & JP 61 271271 A (KANZAKI PAPER MANUFACTURING), 1 December 1986, see abstract -----</p>	1,2,6,11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1, JS 96/17295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2719043	27-10-95	AU-B- 668495	02-05-96
		AU-A- 1651295	16-11-95
		CA-A- 2147807	27-10-95
		EP-A- 0679630	02-11-95
		FI-A- 951967	27-10-95
		JP-A- 8169857	02-07-96
		NO-A- 951545	27-10-95
		PL-A- 308343	30-10-95
		ZA-A- 9502974	19-12-95
US-A-5272156	21-12-93	US-A- 5045551	03-09-91
		US-A- 5183827	02-02-93
		US-A- 5407937	18-04-95
		US-A- 5399561	21-03-95
		US-A- 5534516	09-07-96
		US-A- 5599819	04-02-97
		AT-T- 130297	15-12-95
		AU-B- 627355	20-08-92
		AU-A- 6259190	28-03-91
		CA-A- 2023812	20-03-91
		DE-D- 69023588	21-12-95
		DE-T- 69023588	13-06-96
		EP-A- 0419130	27-03-91
		ES-T- 2079446	16-01-96
		JP-A- 3120274	22-05-91
WO-A-9306086	01-04-93	CA-A- 2119571	01-04-93
		EP-A- 0642499	15-03-95
		FI-A- 941345	23-03-94
		JP-T- 6507178	11-08-94
		PT-A- 100878	29-10-93
US-A-5248823	28-09-93	DE-A- 3903989	20-09-90
		US-A- 5225601	06-07-93
		US-A- 5527945	18-06-96
		AT-T- 143938	15-10-96
		AU-B- 620206	13-02-92
		AU-A- 4926590	16-08-90
		CA-A- 2008042	10-08-90
		DE-D- 59002783	28-10-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/JS 96/17295

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5248823		DE-D- 59010536	14-11-96
		EP-A- 0386452	12-09-90
		EP-A- 0553890	04-08-93
		JP-A- 2270835	05-11-90
		US-A- 5087743	11-02-92

EP-A-722928	24-07-96	FR-A- 2729664	26-07-96
		AU-A- 4079496	15-08-96
		CA-A- 2167651	21-07-96
		JP-A- 8245475	24-09-96
